

REMARKS

The Office Action dated January 12, 2005 has been carefully reviewed and the foregoing amendments are made in response thereto. In view of these amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of pending claims.

I. Status of the Claims

Claims 1-18 and 23 were pending in this application at the time of the Office Action dated January 12, 2005. Claims 8-10 and 12-13 have been amended. Accordingly, claims 1-18 and 23 remain pending and under examination.

II. Amendments to the Claims

Claims 8-10 and 12-13 have been amended. Applicants respectfully submit that no prohibited new matter has been added by way of these amendments. While written description support for the amended claims can be found throughout the specification, specific support for the claim amendments is provided in the table below.

Amended Claim	Support
Claim 8	Page 8, lines 9-28; Page 11, lines 15-19; Original Claims 1 and 8
Claim 9	Original Claim 9
Claim 10	Page 8, lines 9-28; Page 11, lines 15-19; Original Claim 1
Claim 12	Page 22, line 22 to Page 23, line 2; Original Claims 1 and 12

Claim 13	Original Claim 13
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III. Response to the claim objection

Claim 13 was objected to because of the misspelling of *Rickettsia rickettsii*. Claim 13 has been amended to reflect the correct spelling of the name of this organism, therefore, the objection is now moot.

IV. Response to the rejections under 35 U.S.C. §112, second paragraph

Claims 8-12 were rejected under 35 U.S.C. §112 (second paragraph) as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as their invention.

Claims 8-11 were rejected as being indefinite over the recitation of “the minicell strain” because the phrase lacks proper antecedent basis. The claims have been amended to recite “minicell host” from Claim 1. Therefore, this ground for rejection is now moot.

Claims 9 and 12 were rejected as being indefinite over the recitation of “selected from the group comprising” because the claims recite improper format for a Markush group. The claims have been amended to recite a close-ended Markush group. Therefore, this ground for rejection is now moot.

Claim 12 was rejected as being indefinite over the recitation of “the DNA encoding the fusion protein” because the phrase lacks antecedent basis. The claim has been amended to recite “isolating DNA from the gene encoding the fusion protein.” “The gene” refers back to “chimeric gene” of Claim 1. Therefore, the ground for the rejection is now moot.

V. Rejections under 35 U.S.C. §103(a)

Claims 1-10, 12, 14-18 and 23 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over Huang (U.S. Patent No. 5,516,637) in view of Clark-Curtiss (Methods in Enzymology (1983) 101:347-362). As acknowledged by the Examiner, Huang teaches a method of using bacterial cells to express fusion proteins but does not teach the use of minicells. Clark-Curtiss teaches methods for using minicell hosts but does not teach expression of fusion proteins in minicells. The Examiner alleges that one of ordinary skill in the art would be motivated to modify the teaching of Huang so as to have used bacterial minicells in place of bacterial cells to express a fusion protein, because the ordinary artisan would have allegedly recognized based on the disclosure of Clark-Curtiss that fusion proteins in minicells would have been more stable and more easily detected than in bacterial cells. Applicants respectfully traverse this rejection.

First, Applicants respectfully assert that the alleged motivation for combining the Huang and Clark-Curtiss references does not exist. The Examiner purported that the Clark-Curtiss reference teaches that “while recombinant proteins synthesized in bacterial systems are often unstable due to proteolytic degradation, proteins expressed by minicells may be more stable.” Applicants disagree with this characterization of the Clark-Curtiss reference. Clark-Curtiss teaches that certain DNA mutations, such as mutations in the *lon* locus, can confer greater stability on foreign protein expression (page 351, lines 7-17). Clark-Curtiss describes the *lon* locus mutation as decreasing the rate or extent of proteolytic degradation of foreign gene products (lines 14-17). Clark-Curtiss does not teach that such mutations confer greater protein stability in minicells than in bacterial systems possessing the same mutations. The Clark-Curtiss

reference merely describes a mutation which confers greater protein stability in general than in cells without the mutation.

The Examiner also points to page 361 of Clark-Curtiss as providing support for the alleged teaching that proteins expressed in minicells are more stable. The only reference to protein stability on page 361 is a suggestion that minicells may be used to investigate protein stability (see first full paragraph). There is no teaching that proteins expressed in minicells are more stable than those in bacterial cells. Thus, Clark-Curtiss teaches that the *lon* mutation rather than minicell technology alone confers enhanced protein stability. Further, Clark-Curtiss teaches that minicells may be used to study protein instability, suggesting that stability of proteins in minicells is comparable to that in whole cells. Accordingly, while one of ordinary skill in the art might be motivated to use the *lon* mutation in the expression system of Huang to achieve greater stability, one would not have been motivated to use minicells for the methods of Huang based on the disclosure of Clark-Curtiss.

Second, the Clark-Curtiss reference actually teaches away from combining the Huang and Clark-Curtiss references. Clark-Curtiss teaches “that not all protein-synthesizing systems function in minicells and that some systems function less well in minicells than in vegetative cells.” Clark-Curtiss suggests that this “may be due to nuclease or ribonuclease activity in minicells” (page 359, lines 36 to page 360, line 1). Based on this teaching, one of ordinary skill in the art would not be inclined to use minicells for the expression system of Huang because Clark-Curtiss teaches that nuclease or ribonuclease activity may interfere with protein expression. The Federal Circuit held that it is improper to combine references where the

references teach away from their combination. See *In re Grasselli*, 218 USPQ 769 (Fed. Cir. 1983).

Claim 11 was rejected under 35 U.S.C. §103(a) as being unpatentable over Huang in view of Clark-Curtiss and further in view of Shivakumar *et al.* (Plasmid. 1979. 2:279-289). Applicants respectfully traverse this rejection. As previously discussed, one of ordinary skill in the art would not be motivated to combine the teachings of Huang relating to expression of fusion proteins in bacterial cells with the teachings of Clark-Curtiss relating to minicells, because Clark-Curtiss teaches away from using minicells for protein expression. The Shivakumar *et al.* reference does not make up for the deficiencies of Huang and Clark-Curtiss. Accordingly, reconsideration and withdrawal of the §103 rejection based on the combination of Huang, Clark-Curtiss and Shivakumar are respectfully requested.

Claims 4 and 13 were rejected under 35 U.S.C. §103(a) as being unpatentable over Huang in view of Clark-Curtiss and further in view of Georgiou (U.S. Patent No. 5,348,867). Applicants respectfully traverse this rejection. As previously discussed, one of ordinary skill in the art would not be motivated to combine the teachings of Huang relating to expression of fusion proteins in bacterial cells with the teachings of Clark-Curtiss relating to minicells, because Clark-Curtiss teaches away from using minicells for protein expression.. The Georgiou reference does not make up for the deficiencies of Huang and Clark-Curtiss. Accordingly, reconsideration and withdrawal of the §103 rejection based on the combination of Huang, Clark-Curtiss and Georgiou are respectfully requested.

In view of the arguments submitted above, Applicants respectfully request
reconsideration and withdrawal of the 35 U.S.C. §103 rejections.


Conclusion

This reply is fully responsive to the Office Action dated January 12, 2005. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted
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